REMARKS

In this Amendment, the status of the claims is as follows: claims 1-20, 39, 47, 55 and 58-62 have been canceled; claims 21-34, 36-38, 40-46, 48-54, 56 and 57 have been amended; claim 35 was previously presented; and new claim 63 has been added. It is submitted that no new matter has been added by virtue of the amended and new claims, which are supported by the disclosure and claims of the application as originally filed and by the previously presented claims.

More specifically, support for amended claim 65 is found in prior claim 39.

Accordingly, claims 21-38, 40-46, 48-54, 56, 57 and 63 are currently pending in this application.

The claims fulfill the requirements of 35 U.S.C. § 103 (a)

Claims 21-46, 48-54, 56 and 57 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Muller et al. in view of U.S. Patent No. 5,739,152 to Andersson et al. (hereinafter "the '152 patent" or "Andersson et al."). Although the Examiner does not specify the citation for the Muller et al. reference in the instant Office Action, Applicants surmise, based on a review of the file papers, that this rejection is made in view of U.S. Patent No. 5,858,410 to R.H. Muller et al. (hereinafter "the '410 patent" or "Muller et al.") and thus address this reference hereinbelow.

According to the Examiner, Muller et al. teaches a nanosuspension comprising 0.001-30% lecithin, the compounds polyvinyl alcohol, poloxamer, glucose, mannose, trehalose and sorbitol at 0.1-2% and 0.1-30% active, and discloses parenteral, intramuscular and subcutaneous administration; antimycotic, corticoid and immunotherapeutics, e.g., cyclosporin; and autoclaving. Andersson et al. is stated to teach autoclaving a dispersion of active agent under nitrogen to "get a composition stable". The Examiner opines that it would have been obvious for one of ordinary skill in the art to improve the stability of the Muller et al. suspension by autoclaving under nitrogen in view of Anderson et al.

Applicants respectfully disagree that Muller et al. teaches compositions or suspensions that are like those presently claimed by Applicants. Applicants' present claims, considered in their entirety, are directed to compositions and suspensions that are patentably distinct from those of Muller et al.

Applicants' claimed compositions and suspensions particularly comprise a biologically active substance that is water insoluble or poorly soluble, one or more phospholipid surface modifiers and a water-soluble polyhydroxy thermoprotecting agent. In the compositions and suspensions of Applicants, the ratio of the biologically active substance to the phospholipid surface modifier is about 3:1 to about 5:1. Moreover, Applicants' claimed compositions and suspensions are devoid of (i) surfactants that require the addition of a cloud point modifier to elevate their cloud point temperature and (ii) surfactant additives that coagulate on steam sterilization. In addition, Applicants have surprisingly discovered that compositions and suspensions comprising the claimed components act together to achieve the functional properties that are newly attributed to Applicants' compositions and suspensions. (See, Applicants' disclosure at pages 2-4, Description of the Invention, through the penultimate paragraph on page 4). Thus, Applicants' claimed compositions and suspensions do comprise actives and phospholipid surface modifiers and thermoprotecting agents, but at the same time they do not comprise the above-described particular types of surfactants as plainly disclosed in Applicants' specification and in the presently claimed invention.

By contrast, Muller et al. teaches and contemplates nanosuspensions that do not contain the same components, or the same ratios of components, as do the compositions and suspensions of Applicants. Muller et al. generally teaches that the nanosuspensions disclosed and contemplated in the '410 patent contain a variety of surfactants or stabilizers (Col. 7, line 30 to Col. 8, line 18) and various drugs (medicaments), (Cols. 8-11). Muller et al. does not recognize or teach any distinction among the types of surfactants that can be used together in the nanosuspensions described in the '410 patent. Moreover, Muller et al. teaches, discloses and exemplifies nanosuspensions containing components that are distinctly different and patentably distinct from the components that constitute Applicants' presently claimed compositions and suspensions. Thus, unlike Applicants in their presently claimed invention, Muller et al. does not

recognize the particular admixture of components and their functional relationships in suspensions to achieve a particle size increase of no more than two-fold during and after steam sterilization and to create stable, non-flocculated, non-agglomerated, microparticle-containing compositions.

Turning specifically to the sixteen (16) Examples set forth in the Muller et al. patent, it is submitted that fifteen (15) of the Examples describe nanosuspension preparations, and all fifteen preparations are distinctly different from the compositions and suspensions claimed by Applicants. Not one of the nanosuspension preparations described by Muller et al. contains the combination of components and/or the ratios of particular components as described by Applicants in the presently claimed compositions and suspensions.

Illustratively, the nanosuspension described in Example 1 of Muller et al. contains an active (i.e., RMKP 22), and Tween 80 surfactant. This nanosuspension contains neither a phospholipid surface modifier nor a thermoprotecting agent. Because the nanosuspension of Muller et al. does not contain a phospholipid surface modifier, a ratio of about 3:1 to about 5:1 active substance to phospholipid surface modifier is, in turn, absent.

Similarly, the nanosuspensions described in Examples 2, 3, 6, 8, 11 and 12 of Muller et al. contain no phospholipid surface modifier, and thus a ratio of about 3:1 to about 5:1 active substance to phospholipid surface modifier is absent in Muller et al.'s nanosuspensions. The nanosuspension preparation described by Muller et al. in Example 4 also does not contain a phospholipid surface modifier, nor does it achieve the ratio of active to phospholipid surface modifier in accordance with the presently claimed invention. Example 5 of Muller et al. describes a nanosuspension preparation that does not contain a thermoprotecting agent and which provides a ratio of active to phospholipid that is outside the ratios provided by Applicants' presently claimed invention; thus Muller et al. is distinct from the compositions and suspensions described and claimed by Applicants. In Examples 9 and 10 of Muller et al., none of the recipes for the disclosed nanosuspensions contain the components of Applicants' presently claimed invention; recipes A and B lack phospholipid surface modifiers and recipe C lacks a thermoprotecting agent. Example 13 of Muller et al. contains no surfactant, no phospholipid surface modifier, but instead contains sodium carboxymethylcellulose. Examples

14-16 of Muller et al. describe nanosuspension preparations that contain no thermoprotecting agent, in contrast to the compositions and suspensions described and claimed by Applicants.

Thus, it is submitted that the '410 patent to Muller et al. both generally and specifically describes distinct and different nanosuspensions that have specified ingredients and properties, and that do not contain the ingredients, and amounts and functions thereof, as described by Applicants in the presently claimed invention. It is further submitted that Muller et al. is silent regarding a weighted mean particle size increase of not more than two-fold during and after steam sterilization as discovered and presently claimed by Applicants. Accordingly, the '410 patent contemplates, teaches and exemplifies different and distinct nanosuspensions that neither make obvious nor negate the patentability of Applicants' presently claimed invention.

The '152 patent to Andersson et al. teaches pharmaceutical oil-in-water emulsions requiring a dihydropyridine compound, a lipid phase and an emulsifier. These emulsions are contemplated for short-acting (i.e., half life in plasma less than 30 minutes) antihypertensive dihydropyridines. (Col. 1, lines 64-65). Andersson et al. discloses that vials containing emulsions are autoclaved; autoclaving is stated to be optional at Col. 6, lines 29-30. Andersson et al. does not contemplate suspensions comprising particles having a weighted mean particle size that does not increase more than two-fold during and after terminal steam sterilization. Andersson et al. also does not teach or suggest the compositions and suspensions as disclosed and presently claimed by Applicants. Moreover, Andersson et al. does not teach or disclose ratios of an active substance to a phospholipid surface modifier as specified by Applicants.

Andersson et al. does not compensate for the deficiencies and lack of teaching found in Muller et al., and a combination of Muller et al. and Andersson et al. does not make obvious Applicants' presently claimed invention. Considered in its entirety, Applicant's claimed invention is patentably distinct from the teachings of both of these cited references, either alone or in combination. Were one to combine the disparate teachings of Muller et al. and Andersson et al., one would not arrive at Applicants' presently claimed invention because neither of these references teaches or recognizes Applicants' compositions and suspensions comprising combined components with quantitative relationships and their interactive functions, as discovered and presently claimed by the Applicants.

Because of the distinct nature of the teachings of Muller et al., Andersson et al. and the present invention, the teachings of the cited art are insufficient to suggest to, or to motivate, one having skill in the art to make the modifications necessary to arrive at Applicants' compositions and suspensions as presently claimed. The optional teaching found in Andersson et al. to autoclave a preparation in a vial under nitrogen, combined with the patentably distinct nanosuspensions of Muller et al., do not lead one skilled in the art to arrive at Applicants' invention without the very teachings that are provided to the art by the Applicants' own disclosure and inventive discovery.

In view of the foregoing discussion, it is submitted that the present invention is patentably distinct from and unobvious over the cited references. Applicants therefore respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

The Examiner has remarked that the items that were lined-through in the returned PTO Form 1449 were in languages other than English. Applicants point out that for a number of the non-English citations, a cross-reference to the English document was set forth with the name of the foreign patent document in the PTO 1449 Forms submitted with the Information Disclosure Statement dated March 21, 2003.

Notwithstanding, Applicants provide herewith for the Examiner's convenience, copies of English language equivalents of the lined through references from the above-mentioned PTO 1449 Forms.. In particular, the following table lists (i) the number of the reference in the previously submitted PTO 1449 Forms, (ii) the cited document that was not in the English language and (iii) the document which is being submitted herewith as an English equivalent of the cited document. In addition, a clean copy of the previously filed PTO 1449 Forms (and March 21, 2003 IDS) is provided for initialing by the Examiner, to be returned with the next communication from the US P.T.O.

Doc. No. of IDS submitted on March 21, 2003	Application or Patent Number listed in IDS submitted on March 21, 2003	English Language Equivalent
146	DE 2 513 797	U.S. Patent No. 4,056,635
147	DE 2 938 807	U.S. Patent No. 4,280,996
148	DE 3 421 468	U.S. Patent No. 4,880,634
149	EP 0 052 322	English Abstract and Claims
152	EP 0 330 532	U.S. Patent No. 4,895,726
154	EP 0 418 153	U.S. Patent No. 5,100,591
155	EP 0 456 670	English Abstract and Claims
156	EP 0 456 764	English Abstract and Claims
158	EP 0 570 829	U.S. Patent No. 5,527,537
161	EP 0 724 877	U.S. Patent No. 5,880,148
162	EP 0 757 911	U.S. Patent No. 5,827,536
163	EP 0 605 497	English Abstract and Claims
169	JP 55141407	U.S. Patent No. 4,309,421
170	JP 56167616	U.S. Patent No. 4,340,594
171	JP 60208910	U.S. Patent No. 4,687,762
172	JP 63222915	EP 0 272 091 B2

For completeness, Applicants submit herewith a Supplemental Information Disclosure Statement ("IDS") that lists as item "C" in the accompanying PTO 1449 Form the International Search Report for PCT International Application No. PCT/US1999/11888, corresponding to the present application. The documents listed in the PTO 1449 Form accompanying the Supplemental IDS are also listed in the International Search Report for the PCT/US1999/11888 application.

It is submitted that the German patent document, DE 44 40 337, listed as item "B2" in the PTO 1449 Form of the Supplemental IDS, has as its English equivalent U.S. Patent No. 5,858,410 to R.H. Muller et al., which is of record in the instant application. Because U.S. Patent No. 5,858,410 is of record in the application, Applicants have not included this patent in the accompanying Supplemental IDS.

It is further noted that two references listed in the International Search Report (i.e., item "C" in the Supplemental IDS submitted herewith) were previously submitted in Applicants' earlier-filed IDS. These references, which are not submitted with the Supplemental IDS to avoid redundancy, are the following:

U.S. Patent No. 5,100,591 (Doc. No. 87 in the IDS submitted on March 21, 2003); and

U.S. Patent No. 5,663,198 (Doc. No. 121 in the IDS submitted on March 21, 2003).

Consideration of this Supplemental IDS is respectfully requested.

CONCLUSION

Applicants respectfully submit that the present application is now in condition for allowance. An action progressing this application to issue is courteously urged.

Should any additional fees be deemed to be properly assessable in this application for the timely consideration of this Amendment, or during the pendancy of this application, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. **50-0311**; Reference No. **28069-523**; Customer No. **35437**.

If the Examiner believes that further discussion of this application would be helpful, he is respectfully requested to telephone the applicants' undersigned representative at (212) 692-6742 and is assured of full cooperation in an effort to advance the prosecution of the instant application and claims to allowance.

Respectfully submitted,

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